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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,095	02/23/2004	Mark Peakman	4483-4	3528

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,095	PEAKMAN, MARK	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/08/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending and under examination.

Priority: The instant application was filed February 23, 2004. This application claims foreign priority to GB0402129.1, filed January 30, 2004. The foreign application has not been submitted; therefore, the priority date is the filing date, February 23, 2004.

Specification

The disclosure is objected to because of the following informalities: on pg. 1, line 31, the patent application "US 6,562,516" should be corrected to "US 5,827,516"; on pg. 2, line 3, the patent application "US 6,526,516" should be corrected to "US 5, 827,516."

Appropriate correction is required.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Peptides of Preproinsulin.

Claim Objections

Claim 14 is objected to because of the following informalities: there is a break within the claim. Appropriate correction is required.

Claims 7-12, 15 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claim reads on a peptide or peptide combination differing from the original peptide by up to and including 4 amino acid alterations (substitutions, deletions, and/or insertions), as well as the addition of one or more amino acids extending from the N-terminus or C-terminus or both of the original peptide. Thus, the claim reads on any amino acid alteration on any residue of any of the peptides and peptide combinations that are possible from claims 1-5. In addition, the amino acid residues extending from the N- and/or C-terminals can encompass an unlimited number. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to amino acid alterations of the disclosed peptide sequences.

> The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,'

> not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, the amount of experimentation is enormous since the number of changes from the specific sequence are large, one of skill in the art would have to make and test each peptide and peptide combination in order to determine if it had the same activity as a key epitope from preproinsulin. The amount of guidance presented is limited to the exact sequence. No discussion is present as to where the changes might be made to SEQ ID NO. 4-6, 9-13. No working examples are presented. They are, of course, not required but they might add to the enablement if present. The nature of the invention is the identification of key epitopes from preproinsulin; the state of the prior art is that several such peptides are known. The ordinary level of skill in this art is very high. The art is notoriously unpredictable. The effect of one or a few conservative substitutions might be somewhat predictable, if the active areas of the molecule were known, but the claim fails to specify which residues need to be changed, deleted, or added. Finally, the claim is very broad in the sense that it encompasses amino acid alterations at any residue, in any combination, as well

as the addition of an unlimited number of amino acids at either or both the N- and C-terminus of the original peptide sequence.

Based on this analysis, the finding of undue experimentation is mandated.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 6 is drawn to a peptide or peptide combinations differing from the original peptide sequence by up to and including 4 amino acid alterations (substitutions, deletions, and/or insertions), as well as the addition of one or more amino acids extending from the N- terminus or C-terminus or both of the original peptide. The claim reads on any type of alteration on any residue of any of the peptides disclosed in claims 1-5. In addition, the N-terminus or C-terminus or both can be extended by an unlimited number of amino acids. The peptides appear to be essential to the function of the invention. The specification does not disclose any working examples of a peptide or a peptide combination comprising amino acid alterations or extensions from the N- and/or C-terminus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 6, 9, 12-13, 15, 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a peptide having a sequence comprising or consisting of the amino acid sequence depicted as SEQ ID NO.9. The claim is indefinite because if the sequence consists of SEQ ID NO.9, then the amino acid sequence is closed and cannot encompass anymore residues. Therefore, in claim 5, other peptides cannot be added in combination to the peptide of claim 1 if consists only of SEQ ID NO.9. Applicants should clarify between the use of "comprising" and "consisting of" in describing the peptide of claim 1.

Claims 3-5 are drawn to peptides having the amino acids as depicted by the relevant SEQ ID Nos. The use of "having" a sequence renders the claim vague and unclear because "having" in common usage may include or contain other things.

Claim 6 is rejected because there is no definition of what constitutes a non-wildtype amino acid sequence in the claim or specification.

Claims 9, 15 are drawn to a tolerance-promoting adjuvant or tolerance promoting cells. Neither the claims nor specification provide a clear definition of what the term tolerance-promoting means.

Regarding claims 12-13, the phrase "about" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "about"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claim 17 is indefinite because there is no clear definition as to the actual number(s) that represents an increased number of interleukin-10 producing cells and a reduced number of interferon-γ producing cells.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-7 are drawn to peptides. Peptides are naturally occurring in cells and exist in nature. The claimed invention does not show the "hand of man." Amending the claim to require that the peptide is purified or isolated would be remedial.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8, 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by anticipated by Chance et al. (WO 9634882). Chance et al. teach polypeptide compounds wherein the peptide sequence comprises a human proinsulin bridging peptide (des(31-53)hPI) which is the sequence depicted as SEQ ID NO.9 of the instant application (p. 7, SEQ ID NO.1, p. 11, SEQ ID NO.3; claim 1). Chance et al. teach that the polypeptide compounds having significant insulin activity can be formulated in

pharmaceutical form for oral or parenteral administration for the therapeutic or prophylactic treatment of diabetes mellitus and/or non-insulin dependent diabetes mellitus (NIDDM) (p. 28, lines 14-19, p. 37, lines 31-35; claims 8). Chance et al. teach that the compounds can be administered in a single daily dose or in multiple doses per day (p. 30, lines 28-30). An effective amount and preferred dose that is administered is in the range of 10-100 ug/kg of active compound (p. 31, lines 13; claim 14). For an adult human, a typical daily dose is from 0.5 to 50 mg (p. 31, lines 14-15; claims 12-13). Chance et al. also teach the secretion of des(31-53)hPI protein into culture media when cells are grown in the presence of glucose (p. 41, lines 12-14; claim 8).

Claims 1, 6, 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Filvaroff et al. (US20020058614A1). Filvaroff et al. teach a SEQ ID NO.13, where residues 22-32 correspond to SEQ ID NO.9 of the instant application, residues 19-36 correspond to SEQ ID NO.5 of the instant application, and residues 13-38 correspond to SEQ ID NO.10 of the instant application (p. 70, SEQ ID NO.13; claims 1, 3-4). Filvaroff et al. teach a SEQ ID NO.13, which contains additional residues from the N-terminus and C-terminus of SEQ ID NO.9, SEQ ID NO.5, and SEQ ID NO.10 of the instant application (p. 70, SEQ ID NO.13; claim 6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meierhoff et al. (Meierhoff et al., 2002. Diabetes Metab. Res. Rev. 18: 367-380) in view of Peakman et al. (Peakman et al. 1999. J. Clin. Inves. 104(10): 1449-1457). Meierhoff et al. disclose autoantibodies specific for islet antigens, such as insulin (IAA) and thyrosine phosphatase-like protein IA-2 have shown to be very useful measures to estimate the risk to develop diabetes (p. 367). Meierhoff et al. disclose a method for measuring the immune response of a person with diabetes by the enzyme-linked immunospot assay (ELISPOT). Meierhoff et al. disclose that ELISPOT assays have been reported to be up to 400 times more sensitive than ELISAs (p. 372). Meierhoff et al. disclose that peripheral blood mononuclear cells (PBMCs) have been investigated for IFN-γ-secreting cells in parallel to proliferation in patients with diabetes mellitus type I (p. 375). Meierhoff et al. do not disclose the PBMCs are cultured with the peptide and peptide combinations of the instant application. The PBMCs are, instead, incubated with an insulin B-chain antigen (p. 375).

Peakman et al. disclose IA-2 derived peptides eluted from HLA-DR4 that are essentially the same as the IA-2 peptides of the instant application. Peakman et al. teach a sequence, IA-2 753-771, that is encompassed by the amino acid sequence SEQ ID NO.12, IA-2 752-775, of the instant application (p. 1453 table 1). Peakman et al. also teaches a sequence, IA-2 854-872, that encompasses the amino acid sequence SEQ ID NO.13, IA-2 853-872, of the instant application and a sequence, IA-2 709-732, that is encompassed by the amino acid sequence SEQ ID NO.11, IA-2 709-736, of the

instant application (p. 1453 table 1). Peakman et al. disclose that six peptides with amino acid sequences based on the 6 core regions of IA-2ic were used to examine peripheral blood T cell responses in IDDM patients (p. 1452). The six consensus peptides representing the 6 core regions are disclosed by Peakman et al. and are representative of SEQ ID NO.11-13 of the instant application (p. 1452-1454).

It would have been obvious to a person having ordinary skill in the art to extract PBMCs from a patient with diabetes mellitus type I, culture the cells with an insulin-peptide, as taught by Peakman et al., to induce T cells to secrete cytokines, and quantify the cellular production of the cytokines by ELISPOT because Meierhoff et al. teach the advantages of using ELISPOT analysis to asses the antigen-specific immune response on a single-cell level with regard to cytokine secretion (claims 10, 16).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 22, 2004

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit 1653